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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,909	07/21/2003	Eileen Tozer	564462005300	7087

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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,909	TOZER ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☒ Claim(s) *189* is/are allowed.

6)☒ Claim(s) *1, 14, 15, 29, 33, 35, 40, 34-45, 48, 49, 87, 188, 192, 203-207, 217, 218, 225-228* is/are rejected.

7)☒ Claim(s) *225* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,14,15,29,33,35,40,42-45,48,49,51,54,56,58,87,106,107,111,113,116,138,143,174,175,177,182,184,187-190,192,203-208 and 215-231.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 42,51,54,56,58,106,107,111,113,116,138,143,174,175,177,182,184,187,190,208,215,216 and 219-224.

FINAL REJECTION

Status of the Application

1. Applicant's response filed October 16, 2006 is acknowledged. Claims 1, 14, 15, 29, 33, 35, 40, 42-45, 48, 49, 51, 54, 56, 58, 87, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187-190, 192, 203-208, and 215-231 are currently pending. Claims 42, 51, 54, 56, 58, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187, 190, 208, 215, 216, 219-224 are withdrawn.

Election/Restrictions

2. Newly submitted claims 229-231 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims recite nucleic acid SEQ ID Nos: different from elected SEQ ID NO: 29. As discussed in the previous restriction requirement, each nucleic acid sequence constitutes an independent and distinct invention, because no common structural core is shared between the different sequences (i.e. they each have different nucleotide sequences). Also, the different nucleic acids have different functional properties (i.e. they encode different proteins).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 229-231 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 42, 51, 54, 56, 58, 106, 107, 111, 113, 116, 138, 143, 174, 175, 177, 182, 184, 187, 190, 208, 215, 216, and 219-224 drawn to an invention nonelected with traverse in Paper No. 20060710. A complete reply to the final rejection must include

cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claim Objections

3. Claim 225 is objected to because of the following informalities: This claim depends from a withdrawn claim (claim 138). Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, 203-207, 217, 218, and 225-228 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP notes, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1996 (Fed. Cir. 1997)."

In the instant case, independent claim 1 recites "an isolated, synthetic, or recombinant nucleic acid comprising a nucleic acid sequence having at least 75% sequence identity to the

nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues." SEQ ID NO: 29 is 687 nucleotides in length. There are approximately 7.2×10^{274} different sequences with 75% identity to the instant SEQ ID NO: 29. This is a very large genus whose members inherently possess different structural and functional properties.

Regarding genus claims, MPEP notes, "For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

"A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be

deemed to have invented invention of any species other than the one disclosed." In re Curtis, 354 F3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)"

Applicant discloses SEQ ID NO: 29, which encodes a green fluorescent protein. Applicant further discloses related nucleic acid sequences (for example, SEQ ID NO: 1-197 (odd SEQ IDs only), but these sequences share a very high level of identity (greater than 75%), and therefore, do not constitute a representative number of species in the very broad genus outlined above. Furthermore, Applicant does not demonstrate that all of the members of even the described narrow subgenus share a common function. The examples on pages 155-159 teach exemplary methods, and the drawings only depict the fluorescence properties of two proteins. Therefore, since Applicant only teaches nucleic acid sequences with a very high level of identity to the instant SEQ ID NO: 29, with little or no teaching as to their functional properties, and presents no discussion in terms of structural or functional characteristics of sequences with only 75% identity to SEQ ID NO: 29, it must be concluded that the requirement to disclose a representative number of species in the broad genus of claim 1 has not been met (see above), and therefore, at the time of filing, Applicant did not have possession of the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 14, 29, 33, 35, 188, and 192 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AF401282 (submitted by Lesser et al. on August 5, 2001; cited previously).

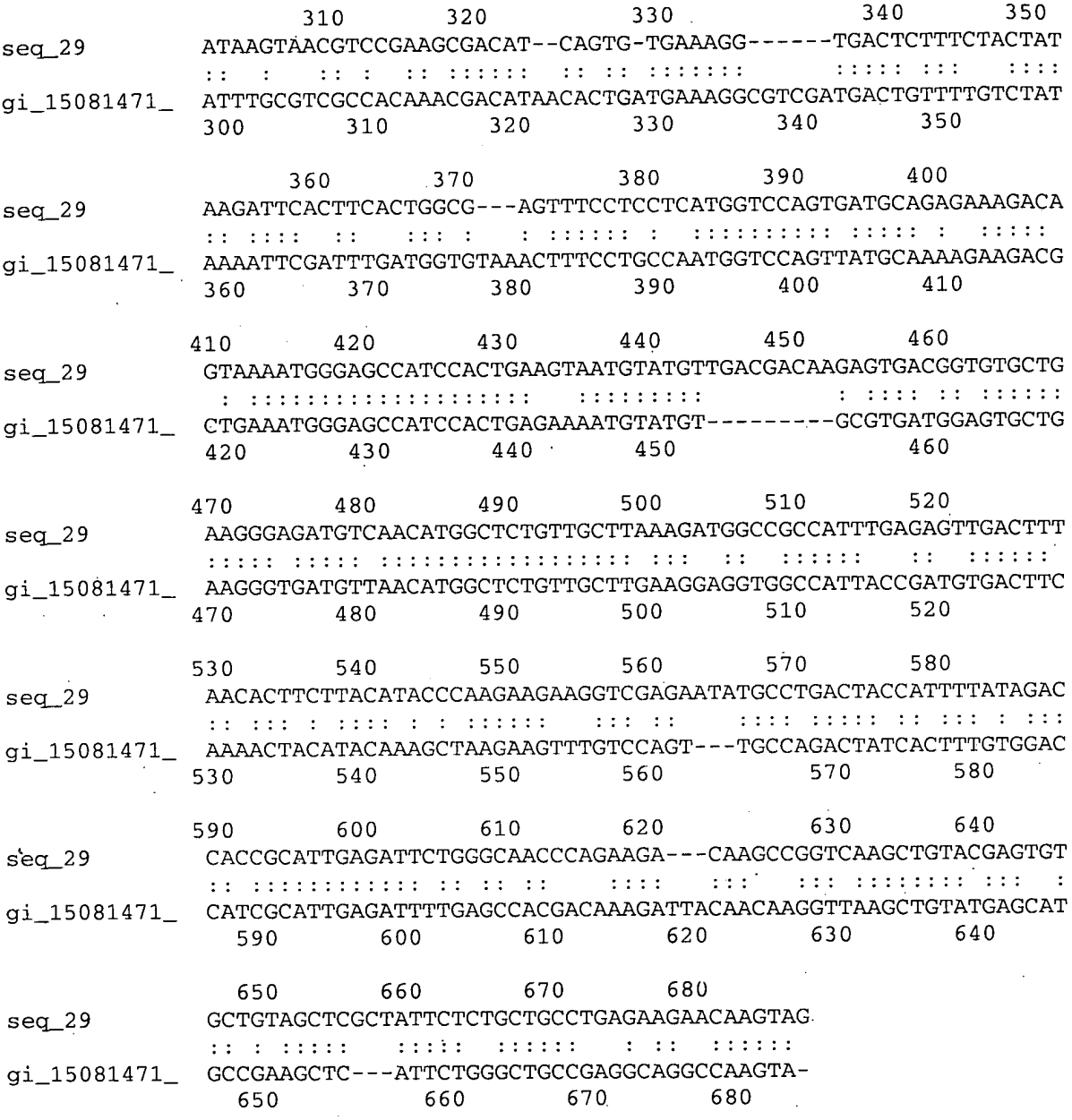
Regarding claim 1, Lesser teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment generated using the BLAST algorithm presented below which demonstrates that Lesser teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 206 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Lesser anticipate the instant claim 1.

```
Score = 83.4 bits (43),  Expect = 1e-12
 Identities = 155/206 (75%), Gaps = 3/206 (1%)
 Strand=Plus/Plus

(SEQ 29)    97 CCTTACGAAGGAACACAGACTTTACATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTT 156
               |||| ||| ||||||||||  |  | |||||||  || ||||||  ||||||| | |||
Lesser     180 CCTTTCGAGGGAACACAGAGCATGGACCTTACAGTCAAAGAAGGCGCGCCTCTGCCTTTT 239

(SEQ 29)   157 TCTTTCGATGTATTGACACCAGCATTTCAGTATGGAAACCGTACATTCACCAAATACCCA 216
                ||| |||| | ||||||  ||| |||  | || || ||| |   |||  ||||||||||
Lesser     240 GCTTACGATATCTTGACAACAGTATTCGATTACGGCAACAGGGTATTTGCCAAATACCCA 299

(SEQ 29)   217 GGCAATATACCAGACTTTTTCAAGCAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGA 276
                   |||||||||||| |||||||||| ||||||   ||  ||||||  ||||||| |||
Lesser     300 CAAGATATACCAGACTATTTCAAGCAGA-CGTTTC--CTGAGGGGTATTCCTGGGAACGA 356

(SEQ 29)   277 AAAATGACTTATGAGGACGGGGGCAT 302
               |  |||||||| ||  |||  ||||||
Lesser     357 AGCATGACTTACGAAGACCAGGGCAT 382
```

Regarding claim 14, the sequence taught by Lesser encodes a green fluorescent protein (see definition).

Regarding claim 29, GenBank Accession No. AF401282 taught by Lesser is 70% identical to the instant SEQ ID NO: 29 (see alignment below). This sequence inherently hybridizes under stringent conditions to the instant SEQ ID NO: 29. Also, as noted above, the sequence taught by Lesser has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 206 nucleotide segment taught by Lesser is about 700 residues).

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
seq_29                                                  687 nt vs.
gi_15081471_gb_AF401282.1_AF401282 Montastraea fa       683 nt
scoring matrix: DNA, gap penalties: -16/-4
70.1% identity;        Global alignment score: 1488

                    10        20        30        40        50        60
seq_29          ATGAAGGGGGTGAAGGAAGTAATGAAGATCAGTCTGGAGATGGACTGCACTGTTAACGGC
                ::::  : : : ::   ::  :::::::::::  :::   :::::  :: :::: :::::
gi_15081471_    ATGAGTGTGATAAAACCAGACATGAAGATCAAGCTGCGTATGGAAGGCGCTGTAAACGGG
                    10        20        30        40        50        60

                    70        80        90       100       110       120
seq_29          GACAAATTTAAGATCACTGGGGATGGAACAGGAGAACCTTACGAAGGAACACAGACTTTA
                 :::: ::   :::    :: :: :::: ::  : :::: ::: ::::::::::   :
gi_15081471_    CACAAGTTCGTGATTGAAGGAGACGGAAAGGGCAAGCCTTTCGAGGGAACACAGAGCATG
                    70        80        90       100       110       120

                   130       140       150       160       170       180
seq_29          CATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTTTCTTTCGATGTATTGACACCAGCA
                 : :::::::  :: ::::::  ::::::: : ::: ::: :::: : :::::: ::: :
gi_15081471_    GACCTTACAGTCAAAGAAGGCGCGCCTCTGCCTTTTGCTTACGATATCTTGACAACAGTA
                   130       140       150       160       170       180

                   190       200       210       220       230       240
seq_29          TTTCAGTATGGAAACCGTACATTCACCAAATACCCAGGCAATATACCAGACTTTTTCAAG
                ::  : :: :: ::: :   :::  ::::::::::    :::::::::::: :::::::
gi_15081471_    TTCGATTACGGCAACAGGGTATTTGCCAAATACCCACAAGATATACCAGACTATTTCAAG
                   190       200       210       220       230       240

                   250       260       270       280       290       300
seq_29          CAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGAAAAATGACTTATGAGGACGGGGGC
                ::::: :::::  : ::  ::::: ::::::: :::: :::::::: :: :::  ::::
gi_15081471_    CAGAC-GTTTCCTGAGG--GGTATTCCTGGGAACGAAGCATGACTTACGAAGACCAGGGC
                    250       260       270       280       290
```



Regarding claims 33 and 35, GenBank Accession No. AF401282 teaches a probe comprising at least 10 consecutive bases of a sequence comprising the instant SEQ ID NO: 29 (see alignment following either claim 1 or claim 29). As noted above, the sequence taught by Lesser has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700

contiguous residues (see alignment presented above following claim 1, where the 206 nucleotide segment taught by Lesser is about 700 residues).

Regarding claim 188, Lesser teaches an isolated, synthetic, or recombinant nucleic acid comprising a sequence encoding a fluorescent protein and having at least about 75% identity to the instant SEQ ID NO: 29 (see alignment following claim 29, where the 70% identity between the Lesser sequence and SEQ ID NO: 29 is about 75%).

Regarding claim 192, the sequence recited in GenBank Accession No. AF401282 encodes a fluorescent protein (see definition) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, the GenBank sequence comprises segments with overhangs that can anneal to each other such as "GGA" which is the start overhang in the segment defined by nucleotides 42-44 and the "stop" overhang in the segment defined by nucleotides 98-100 "CCT" (see alignment following claim 29). Also, as noted above, the sequence taught by Lesser has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 206 nucleotide segment taught by Lesser is about 700 residues).

7. Claims 1, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, and 225-228 are rejected under 35 U.S.C. 102(b) as being anticipated by Lukyanov et al. (WO 01/27150 A2; cited previously).

Regarding claim 1, Lukyanov teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment presented below which demonstrates that Lukyanov

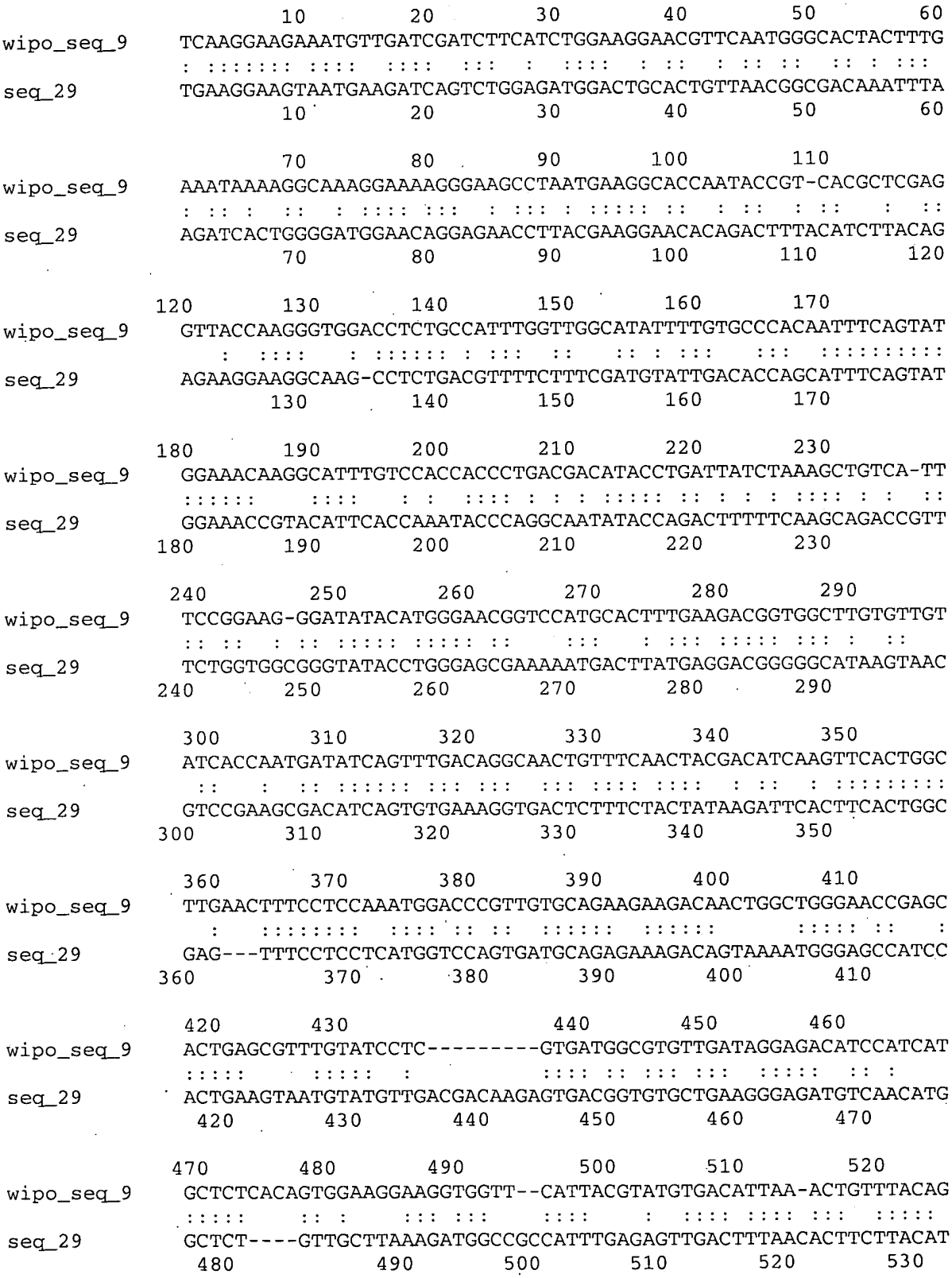
teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 19 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Lukyanov anticipate the instant claim 1.

```
78.9% identity in 19 nt overlap; score:  59 E(10,000): 6.5e+03

          190       200
seq_29    ATGGAAACCGTACATTCAC
          :::: ::: :: ::: :::
Lukyanov  ATGGGAACGGTCCATGCAC
          320       330
```

Regarding claim 15, the nucleic acid sequence taught by Lukyanov encodes a cyan fluorescent protein (see Table 1, page 29, where the emission maximum of SEQ ID No: 9 (dsFP483 is reported to be 483 nm. This value is within the emission range for cyan fluorescent proteins).

Regarding claim 29, Lukyanov teaches a sequence that is 60% identical to the instant SEQ ID NO: 29 (see alignment below). This sequence inherently hybridizes under stringent conditions to the instant SEQ ID NO: 29. Also, as noted above, the sequence taught by Lukyanov has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 19 nucleotide segment taught by Lukyanov is about 700 residues).

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
wipo_seq_9                                          600 nt vs.
seq_29                                              610 nt
scoring matrix: DNA, gap penalties: -16/-4
60.0% identity;        Global alignment score: 747
```


wipo_seq_9 TCAAGGAAGAAATGTTGATCGATCTTCATCTGGAAGGAACGTTCAATGGGCACTACTTTG
seq_29 TGAAGGAAGTAATGAAGATCAGTCTGGAGATGGACTGCACTGTTAACGGCGACAAATTTA
wipo_seq_9 AAATAAAAGGCAAAGGAAAAGGGAAGCCTAATGAAGGCACCAATACCGT-CACGCTCGAG
seq_29 AGATCACTGGGGATGGAACAGGAGAACCTTACGAAGGAACACAGACTTTACATCTTACAG
wipo_seq_9 GTTACCAAGGGTGGACCTCTGCCATTTGGTTGGCATATTTTGTGCCCACAATTTCAGTAT
seq_29 AGAAGGAAGGCAAG-CCTCTGACGTTTTCTTTCGATGTATTGACACCAGCATTTCAGTAT
wipo_seq_9 GGAAACAAGGCATTTGTCCACCACCCTGACGACATACCTGATTATCTAAAGCTGTCA-TT
seq_29 GGAAACCGTACATTCACCAAATACCCAGGCAATATACCAGACTTTTTCAAGCAGACCGTT
wipo_seq_9 TCCGGAAG-GGATATACATGGGAACGGTCCATGCACTTTGAAGACGGTGGCTTGTGTTGT
seq_29 TCTGGTGGCGGGTATACCTGGGAGCGAAAAATGACTTATGAGGACGGGGGCATAAGTAAC
wipo_seq_9 ATCACCAATGATATCAGTTTGACAGGCAACTGTTTCAACTACGACATCAAGTTCACTGGC
seq_29 GTCCGAAGCGACATCAGTGTGAAAGGTGACTCTTTCTACTATAAGATTCACTTCACTGGC
wipo_seq_9 TTGAACTTTCCTCCAAATGGACCCGTTGTGCAGAAGAAGACAACTGGCTGGGAACCGAGC
seq_29 GAG---TTTCCTCCTCATGGTCCAGTGATGCAGAGAAAGACAGTAAAATGGGAGCCATCC
wipo_seq_9 ACTGAGCGTTTGTATCCTC---------GTGATGGCGTGTTGATAGGAGACATCCATCAT
seq_29 ACTGAAGTAATGTATGTTGACGACAAGAGTGACGGTGTGCTGAAGGGAGATGTCAACATG
wipo_seq_9 GCTCTCACAGTGGAAGGAAGGTGGTT--CATTACGTATGTGACATTAA-ACTGTTTACAG
seq_29 GCTCT----GTTGCTTAAAGATGGCCGCCATTTGAGAGTTGACTTTAACACTTCTTACAT

```
                530        540           550        560        570        580
wipo_seq_9      GGCCAAGAAGCCCGTAAAGA---TGCCAGGGTATCACTATGTTGACACCAAACTGGTTAT
                :::::::::    ::  :::    :::: :  :: :: : : : :::  :     : :  ::
seq_29          ACCCAAGAAGAAGGTCGAGAATATGCCTGACTACCATTTTATAGACCACCGCATTGAGAT
                     540        550        560        570        580        590

                     590        600
wipo_seq_9      AAGGAGCAACGACAAAGA
                  : :::::     ::::
seq_29          TCTGGGCAACCCAGAAGA
                     600        610
```

Regarding claims 33 and 35, Lukyanov teaches a probe comprising at least 10 consecutive bases of a sequence of the instant SEQ ID No: 29 (see for example, nucleotides 170-179 in the above alignment: ATTTCAGTAT). This was determined by visual inspection. Also, as noted above, the sequence taught by Lukyanov has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 19 nucleotide segment taught by Lukyanov is about 700 residues).

Regarding claim 40, Lukyanov teaches an amplification primer pair (see page 12, line 32-page 13, line 4) for amplifying a nucleic acid sequence encoding a polypeptide with fluorescent activity (SEQ ID No: 9 of Lukyanov), where the primer pair is capable of amplifying a nucleic acid of claim 1 (Lukyanov teaches a nucleic acid that anticipates claim 1, as noted above).

Regarding claim 43, Lukyanov teaches an expression cassette comprising the nucleic acid of claim 1 (page 10, lines 12-13).

Regarding claim 44, Lukyanov teaches a vector comprising the nucleic acid of claim 1 (page 10, lines 12-17).

Regarding claim 45, Lukyanov teaches that the vector may be a plasmid, phage, or cosmid (page 2, lines 35-36). Lukyanov also teaches the use of viral vectors, phagemids,

fosmids, bacteriophages, and artificial chromosomes (see page 11, and the cited references therein).

Regarding claims 48 and 49, Lukyanov teaches a transformed cell comprising a vector where the vector comprises a nucleic acid of claim 1 (page 10, line 12 – page 11, line 36).

Regarding claim 87, Lukyanov teaches an array comprising the immobilized nucleic acid of claim 1 (page 13, lines 5-14).

Regarding claim 188, Lukyanov teaches an isolated nucleic acid sequence encoding a fluorescent protein (see above) and having at least about 75% identity to SEQ ID No: 29 (see alignment presented following claim 29, where the sequences are 60% identical over the full-length SEQ ID No: 29. This is about 75% identity).

Regarding claim 192, SEQ ID No: 9 of Lukyanov encodes a fluorescent protein (see above) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, SEQ ID No: 9 of Lukyanov comprises segments with overhangs that can anneal to each other such as GGA which is the "start" overhang in the segment defined by nucleotides 32-34 and the "stop" overhang in the segment defined by nucleotides 135-137 "CCT" (see alignment above). Also, as noted above, the sequence taught by Lukyanov has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 19 nucleotide segment taught by Lukyanov is about 700 residues).

Regarding claims 225 and 226, Lukyanov teaches a recombinant nucleic acid encoding a fluorescent protein codon-optimized for expression in a host cell comprising the sequence of

claim 1 (SEQ ID NO: 9 of Lukyanov anticipates the instant claim 1, as discussed above; page 14, lines 3-5 and page 36, lines 1-5 teach codon-optimized forms).

Regarding claim 227, Lukyanov further teaches inclusion of a tag or reporter sequence (page 4, lines 10-12) and also the inclusion of epitope tags (page 9, lines 26-34).

Regarding claim 228, Lukyanov teaches labeled probes (page 12, lines 26-28), and further teaches that the nucleic acids may be labeled with epitope tags (page 9, lines 26-34).

8. Claims 1, 15, 29, 40, 43-45, 48, 49, 188, and 192 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US 6,140,132).

Regarding claim 1, Tsien teaches an isolated, synthetic, or recombinant nucleic acid encoding a fluorescent protein, comprising a nucleic acid sequence having at least 75% sequence identity to the nucleic acid sequence of SEQ ID NO: 29 over a region of at least about 700 contiguous residues. See the alignment presented below which demonstrates that Tsien teaches a sequence with 75% identity to the instant SEQ ID NO: 29 over a region of 17 contiguous residues. As noted above, the phrase "at least about 700 contiguous residues" does not define a minimal number of residues that are "at least about 700 contiguous residues." Therefore, the teachings of Tsien anticipate the instant claim 1.

```
82.4% identity in 17 nt overlap; score:  58 E(10,000): 6.8e+03

         630       640
seq_29 GGTCAAGCTGTACGAGT
       :: : ::::::::: :::
tsien_ GGACGAGCTGTACAAGT
            710
```

Regarding claim 15, SEQ ID NO: 3 and SEQ ID NO: 7 of Tsien encodes a green fluorescent protein and a cyan fluorescent protein, respectively (see Table 5, column 5).

Regarding claim 29, Tsien teaches a sequence that is 51% identical to the instant SEQ ID NO: 29 (see alignment below). This sequence inherently hybridizes under stringent conditions to the instant SEQ ID NO: 29. Also, as noted above, the sequence taught by Tsien has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 17 nucleotide segment taught by Tsien is about 700 residues).

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
seq_29                                                  687 nt vs.
tsien_cfp_seq_7                                         720 nt
scoring matrix: DNA, gap penalties: -16/-4
49.0% identity;        Global alignment score: -11


                          10                  20        30        40
seq_29          ATG------AAGGGGGTGAAG---------GAAGTAATGAAGATCAGTCTGGAGATGGAC
                :::      ::::: : : ::          :  ::  ::   :::    : ::: :::::
tsien_cfp_se    ATGGTGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGAC
                        10        20        30        40        50        60

                   50        60        70        80        90        100
seq_29          TGCACTGTTAACGGCGACAAATTTAAGATCACTGGGGATGGAACAGGAGAACCTTACGAA
                 ::   :: :::::: :::  :: :   :  : :: :: ::    :: ::  :   : :
tsien_cfp_se    GGCGACGTAAACGGCCACAGGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTAC
                        70        80        90       100       110       120

                  110       120       130       140       150       160
seq_29          GGAACACAGACTTTACATCTTACAGAGAAGGAAGGCAAGCCTCTGACGTTTTCTTTCGAT
                :: :  : :::  :  :  : :     :     :::::::  :   :::   ::  :
tsien_cfp_se    GGCAAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCC--CGTGCCCTGGCCCA
                       130       140       150       160         170

                  170       180       190       200       210       220
seq_29          GTATTGACACCAGCATTTCAGTATGGAAACCGTACATTCACCAAATACCCAGGCAATAT-
                  : :  :::: : :  :     :    : :: : :::: :   ::::: : : : ::
tsien_cfp_se    CCCTCGTGACCACCCTGACCTGGGGCGTGCAGTGC-TTCAGCCGCTACCCCGACCACATG
               180       190       200       210       220       230
```

```
                    230       240       250       260       270
seq_29          -ACCAG----ACTTTTTCAAGCAGACCGTTTCTGGTGGCGGGTATACCTGGGAGCGAAAA
                 : :::    :::: ::::::    :: :  : :  :::   ::   :  :::::: :
tsien_cfp_se    AAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGC---TACGTCCAGGAGCGCACC
                240       250       260       270           280       290

              280       290       300       310       320       330
seq_29          ATGACTTATGAGGACGGGGGCATAAGTAACGTCCGAAGCGACATCAGTGTGAAAGGTGAC
                ::    :   ::::::  ::::     ::   :::   :::  : :   :  : :: :::
tsien_cfp_se    ATCTTCTTCAAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGAC
                   300       310       320       330       340       350

              340       350       360         370       380       390
seq_29          TCTTTCTACTATAAGATTCACTTCA--CTGGCGAGTTTCCTCCTCATGGTCCAGTGATGC
                 :   ::  :    ::  : : ::   :::  : :  ::  : ::: ::   :  :   :
tsien_cfp_se    AC--CCTGGT----GAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAAC
                     360           370       380       390       400

                400       410       420       430          440
seq_29          AGAGAAAGACAGTAAAATGGGAGCCATCCACTGAAGT---AATGTATGTT-----GACGA
                :      : ::  ::  :::    :: : ::   ::    :: :: : :       : :::
tsien_cfp_se    ATCCTGGGGCAC-AAGCTGGAGTACAACTACATCAGCCACAACGTCTATATCACCGCCGA
               410       420       430       440       450       460

              450       460       470       480       490       500
seq_29          CAAGAGTGACGGTGTGCTGAAGGGAGATGTCAACATGGCTCTGTTGCTTAAAGATGGCCG
                ::::    :    :   : ::::   :  :::: ::     :      :  : :: ::: :
tsien_cfp_se    CAAGCAGAAGAACGGCATCAAGGCCCACTTCAAGATCCGCCACAACATCGAGGACGGCAG
                470       480       490       500       510       520

              510       520       530       540       550         560
seq_29          CCATTTGAGAGTTGACTTTAACACTTCTTACATACCCAA-GAAGAAGGTC--GAGAATAT
                :     :   :  :::    ::        :::  ::::  :  :: :: : . : :    :
tsien_cfp_se    CGTGCAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCT
                530       540       550       560       570       580

                 570       580       590       600       610         620
seq_29          GCCTGACTACCATTTTATAGACCACCGCATTGAGATTCTGGGCAA---CCCAGAAGACAA
                ::: ::: :::: :   : :: :::: :: :  :   ::: ::::   :::  : :: ::
tsien_cfp_se    GCCCGACAACCACTACCT-GAGCACC-CAGTCCGCC-CTGAGCAAAGACCCCAACGAGAA
                590       600       610       620       630       640

                     630           640          650       660          670
seq_29          GC-CGGTCAAGCTGTAC-----GAGT--GTG-CTGTAGCTCGCTAT---TCTCTGC-TGC
                :: :: :::    :: :     ::::  ::: : :  :: ::  ::   :::: :: ::
tsien_cfp_se    GCGCGATCACATGGTCCTGCTGGAGTTCGTGACCGCCGC-CGGGATCACTCTCGGCATGG
                   650       660       670       680       690       700

                      680
seq_29          CTGAGAAGAACAAGTAG
                  :::  : :::::::
tsien_cfp_se    ACGAGCTGTACAAGTAA
                    710       720
```

Regarding claim 40, Tsien teaches an amplification primer pair for amplifying a nucleic acid sequence encoding a polypeptide with fluorescent activity (column 11, lines 41-46), where the primer pair is capable of amplifying a nucleic acid of claim 1 (Tsien teaches a nucleic acid that anticipates claim 1, as noted above).

Regarding claim 43, Tsien teaches an expression cassette comprising the nucleic acid of claim 1 (column 11, line 57 – column 12, line 40).

Regarding claim 44, Tsien teaches a vector comprising the nucleic acid of claim 1 (column 11, line 66 – column 12, line 40).

Regarding claim 45, Tsien teaches that the vector may be a plasmid, phage, cosmid viral vectors, bacteriophages, and artificial chromosomes (column 13, lines 45-63).

Regarding claims 48 and 49, Tsien teaches a transformed cell comprising a vector where the vector comprises a nucleic acid of claim 1 (column 13, lines 45-63).

Regarding claim 188, Tsien teaches an isolated nucleic acid sequence encoding a fluorescent protein (see above) and having at least about 75% identity to SEQ ID No: 29 (see alignment presented following claim 29, where the sequences are 49% identical over the full-length SEQ ID No: 29. This is about 75% identity).

Regarding claim 192, SEQ ID No: 7 of Tsien encodes a fluorescent protein (see above) and also has a sequence comprising a combination of segments whose overhangs as described in Figure 15 can anneal to each other. Specifically, SEQ ID No: 7 of Tsien comprises segments with overhangs that can anneal to each other such as GGA which is the "start" overhang in the segment defined by nucleotides 18-20 and the "stop" overhang in the segment defined by nucleotides 116-118 "CCT" (see alignment following claim 29). Also, as noted above, the

sequence taught by Tsien has 75% identity to the instant SEQ ID NO: 29 over a region of at least about 700 contiguous residues (see alignment presented above following claim 1, where the 17 nucleotide segment taught by Tsien is about 700 residues).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 217 and 218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lukyanov et al. (WO 01/27150; cited previously) in view of Short (WO 00/77262 A1; cited previously).

Lukyanov teaches a nucleic acid sequence (SEQ ID NO: 9) that anticipates the instant claim 1, as discussed above.

Lukyanov teaches that the nucleic acid may be obtained using non-stochastic site-directed mutatgensis methods (page 13, line 15 – page 14, line 2), but does not teach generation of the recombinant nucleic acid by synthetic ligation reassembly.

Regarding claim 218, Lukyanov teaches expression of recombinant proteins (page 13, line 15 – page 14, line 2).

Short teaches a directed evolution method for evolving nucleic acids encoding novel or improved proteins (see abstract).

Regarding claim 217, Short teaches that standard non-stochastic mutagenesis methods are limited, because only a small number of new variant products are generated with each application of the methods and the types of mutations possible are also limited (see page 4, lines 15-20). Short teaches that synthetic ligation reassembly represents an improvement over these standard non-stochastic site-directed mutagenesis methods, because: (1) it generates a larger number of products with predetermined (non-random) structures with each application; (2) it readily generates more types of mutant polynucleotides, thereby generating a resulting group of mutant products with greater diversity; (3) background resulting from undesired products is decreased; (4) saturation or exhaustive mutagenesis is possible; and (5) the products are produced in a systematic, predetermined fashion (see page 5, lines 1-10).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the synthetic ligation reassembly method taught by Short to generate recombinant versions of the nucleic acids of Lukaynov. Lukaynov expressly taught production of recombinant polynucleotides using site-directed mutagenesis techniques in order to obtain polynucleotides encoding proteins with improved properties (see page 13, lines 13-31). Since

Short taught that synthetic ligation reassembly offered distinct advantages over the conventional methods suggested by Lukaynov, namely the ability to more efficiently and accurately generate a larger number of different, more diverse product sequences (see above), the ordinary practitioner would have been motivated to utilize this method in order to obtain a faster, simpler method of generating a large variety of mutant polynucleotides.

Allowable Subject Matter

11. Claim 189 is allowed.

Response to Arguments

12. Claim Objections

Applicant's arguments, see page 17, filed October 16, 2006, with respect to the objections to claims 219 and 220 have been fully considered and are persuasive. These objections have been withdrawn.

Rejections under 35 U.S.C. 112, 1st paragraph

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that the disclosure teaches a representative number of species, and particularly cites those sequences recited in the instant claims 215, 216, 220, 224, and 229 as exemplary sequences within the claimed genus. This argument was not found persuasive, because although these claims disclose numerous sequences with identity to SEQ ID NO: 29 ranging from 72% (SEQ ID NO: 169 disclosed in claim 224) to 99.6% (SEQ ID NO: 17,

disclosed in claim 208), the functional properties of the vast majority of the proteins encoded by these different sequences have not been determined. As noted above, the fluorescence properties of only two proteins (SEQ ID NO: 8 and SEQ ID NO: 18) were measured by fluorescence spectroscopy (See Figures 11-14). Also, Table 2 in the specification recites excitation and emission wavelengths for a number of proteins encoded by nucleic acid sequences of the invention, but it is not clear whether these are predicted or experimentally determined values. As discussed above, an enormous number of sequences (7.2×10^{274}) possess 75% identity to the instant SEQ ID NO: 29 over 700 contiguous residues. Although Applicant has demonstrated possession of the genus of nucleic acid sequences displaying at least 95% identity to the instant SEQ ID NO: 29, Applicant has not demonstrated possession of the claimed genus of sequences having only 75% identity to the instant SEQ ID NO: 29. Therefore, the rejection of claims 1, 14, 15, 29, 33, 35, 40, 43-45, 48, 49, 87, 188, 192, 203-207, 217, 218, and 225-228 as lacking adequate written description under § 112, 1st paragraph has been maintained.

Rejections under 35 U.S.C. 102

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that none of the previously applied references (Lesser, Lukaynov, Tsien) teach all of the elements of the amended claims (see pages 19-20 of the response). This argument was not found persuasive, because as discussed above, the phrase "at least about 700 contiguous residues" appearing in amended claim 1 and the phrase "at least about 75% identity" appearing in claim 188 renders these claims indefinite. The use of the phrase "at least about" results in complete uncertainty as to the minimum number of contiguous residues or percent

identity encompassed by the claims, and the specification does not cure this deficiency by explicitly defining these phrases. Therefore, in the absence of a clearly defined minimum boundary for the required percent identity or stretch of contiguous residues, the prior art of Lesser, Lukaynov, and Tsien continues to anticipate the instant claims. These rejections are maintained.

Rejections under 35 U.S.C. 103

Applicant's arguments filed October 16, 2006 have been fully considered but they are not persuasive. Applicant argues that Lukaynov does not teach all of the elements of the amended claim 1 and Short does not remedy this deficiency in the primary reference (page 20 of the response). This argument was not found persuasive, because as discussed above, the Lukaynov does teach a nucleic acid anticipating the instant claim 1. The Short reference is only relied upon for its teachings regarding synthetic ligation reassembly. Therefore, the rejection of claims 217 and 218 as obvious in view of the combined teachings of Lukaynov and Short is maintained.

Conclusion

With the exception of claim 189 (allowable over the art), the claims are free of the art, but have been rejected for other reasons, as noted above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
December 18, 2006

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
12/20/06